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EXAMINER
KERR, KATHLEEN M

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 12/31/2002 10

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/768,479	Applicant(s) CORNISH, VIRGINIA W.	
	Examiner Kathleen M Kerr	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *91-133* is/are pending in the application.

4a) Of the above claim(s) *128-133* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *91-105 and 111-127* is/are rejected.

7)☒ Claim(s) *106-110* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4,6,7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Application Status

1. In response to the previous Office action, a written restriction requirement (Paper No. 8, mailed on September 5, 2002), Applicants filed an election received on October 15, 2002 (Paper No. 9). Thus, Claims 91-133 are pending in the instant Office action.

Election

2. Applicant's election with traverse of Group I, Claims 91-127, species in Claim 107 in Paper No. 9 is acknowledged. The traversal is on the ground(s) that all the processes of Group II require the particulars of Group I. This is not found persuasive because of the reasons cited for distinctness of the inventions previously. Applicant cites rejoinder practice in traversal of the instant rejection; such practice is only utilized when product claims are allowable. Applicant argues that the inventions are not independent; the Examiner does not disagree. The Examiner previously noted that the inventions were distinct. Applicant also argues that the burden to examine the Groups together would be minimal. The Examiner disagrees based on the distinct class/subclass classifications of the elected Group with respect to the method Groups. Applicant also argues the election of species since all the compounds of the genus require methotrexate (MTX) as a part of the compound. This is not persuasive because MTX is not novel, and searching more than just a common, but old, compound will not effectively search the invention.

The requirement is still deemed proper and is therefore made FINAL. Claims 128-133 are withdrawn from consideration as non-elected inventions. Claims 91-127 will be examined herein.

Priority

3. The instant application is granted the benefit of priority for the continuation-in-part U.S. non-Provisional Application No. 09/490,320 as requested in the declaration and the first lines of the specification.

Information Disclosure Statement

4. The information disclosure statements filed on June 2, 2001 (Paper No. 4) June 11, 2002 (Paper No. 6), and August 20, 2002 (Paper No. 7) have been reviewed, and their references have been considered as shown by the Examiner's initials next to each citation on the attached copy. Numerous corrections have been made on Paper Nos:4 and 6 for appropriate and complete listing of the references on the front of a patent publication that should result from the instant application. Moreover, the Search Report cited on Paper No. 4 has been considered, but crossed out since it is not printed on the face of a patent.

Drawings

5. The drawings have been approved by the Draftsmen and are, therefore, entered as formal drawings acceptable for publication upon the identification of allowable subject matter.

Objections to the Specification

6. The specification is objected to for lacking updated continuity data in the first paragraph. The instant application claims the benefit of U.S. non-Provisional Application No. 09/490,320 filed on January 24, 2000 and now abandoned. Appropriate amendment to the specification is required (see M.P.E.P. § 201.11).

7. In the specification, the Abstract is objected to for not completely describing the disclosed subject matter (see M.P.E.P. § 608.01(b)) and for having an improper title and structure. The Abstract must be entitled "Abstract" or "Abstract of the Disclosure" as it described the entirety of the specification and not just the invention in the claims. The Abstract must be a single paragraph. Moreover, it is noted that in many databases and in foreign countries, the Abstract is crucial in defining the disclosed subject matter, thus, its completeness is essential. The Examiner suggests the inclusion of dexamethasone and methotrexate as two integral "handles" in the disclosure hybrid assay system.

8. The specification is objected to for having improperly cited references.

a) Beginning on page 62, the references are inconsistent in their citation with bold and italics used without clarity. Some references contain titles while others do not.
b) If two or more publications are listed by the same author in the same year (Belshaw, Galleni, Stemmer, and Stockwell), the designation "a, b, c" after the publication year is required to distinguish between the citations.
c) On page 62, the Bolin reference is incorrect; Filman is the first author and Hamlin is not an author.
d) On page 63, the Caldwell reference is incomplete without a title.
e) On page 63, the DeGrado reference notes "and following articles" which is inappropriate in a reference section.
f) On page 67, the Lin reference in preparation must have a completed reference at this time. Correction on the publication date in the specification is also required on page 40.
g) On page 68, the reference starting "*The chemistry of b-lactams*" is inappropriately cited.
h) Throughout the specification, references are improperly cited by only the author; a publication year must be included with each reference throughout the specification for clarity.

Appropriate correction for each point above is required.

Objections to the Claims

9. Claim 91 is objected to for spelling "methorexate" incorrectly; the correct spelling is ---methotrexate---as found throughout the specification.

10. Claim 127 is objected to for having improper punctuation; the comma after "cerevisiae" is inappropriate.

11. Claims 106-110 are objected to as depending from rejected claims.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 91-93, 97-105, and 111-127 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In Claims 91-93, the term analog is used with respect to either methotrexate or dexamethasone and is unclear as to its metes and bounds. Both of these are complex structures with many side groups; the breadth of the term "analog" is wholly unclear. Moreover, are these structural analogs or functional analogs or both? Clarification is required.

13. Claims 92-105 and 111-127 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following abbreviations are not defined upon their first

appearance in the claims: Dex, Mtx, LexA, and B42. Appropriate clarification is required. The Examiner suggests the following: ---dexamethasone (Dex)--- upon its first appearance in the claims where thereafter the abbreviation may be used alone. Correction is required.

14. Claims 119 and 121 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The parentheses around "DNA-binding domain" and "transcription activation domain" are unclear in their meaning.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

15. Claims 91-94, 97-105, 111-122, and 125-127 are rejected under 35 U.S.C. § 112, first paragraph, written description, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The instant claims are drawn to compounds, complexes comprising said compounds, or cells comprising said complexes wherein the compounds are described by sub-compounds using functional language alone without any particular, clear structural limitations. This includes the H1 moiety without a clear definition of a methotrexate analog as noted above in the rejection under 35 U.S.C. § 112, second paragraph and the H2 moiety.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." University of California v. Eli Lilly and Co., 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed correlation between function and structure, or a combination of these.

In the instant specification, dimerizing compounds are generally described as comprising two ends (H1 and H2) and a linker (Y) wherein the two ends each recognize different proteins and/or receptors. Specific examples of such compounds are also described using receptor-recognizing agents (i.e., ligands) like methotrexate, which recognizes dihydrofolate reductase (DHFR), and dexamethasone, which recognizes rat glucocorticoid receptor (rGR). The art is replete with examples of receptor-recognizing agents or ligands; however, no generic structure can be described to encompass the entire genus. While the linker region is adequately described since its function is limited, any structure "capable of binding to a receptor" is an extremely broad genus that lacks adequate written description in the instant specification. No identifying, general characteristics of receptor-binding compounds are disclosed; only examples are offered.

Thus, one of skill in the art would be unable to predict the structures of other dimerizing compounds that meet the limitations of the claims based on description in the instant specification and the knowledge in the art.

Specific to Claims 97-105 and 113-118 is an issue concerning written description as related to a specific function. The instant claims are drawn to ligands having a particular affinity (IC50) for its receptor and/or protein. No particular structure is correlated with such an affinity, other than by way of example. Thus, it would be impossible for one of skill in the art to predict the subset of ligands that will bind to their receptors and/or proteins with an affinity of 1 nM, for example, as claimed in Claim 105.

Specific to Claims 111 and 125-127 is an issue concerning written description as related to a specific function. The instant claims are drawn to complexes comprising fusion proteins that contain "a binding domain capable of binding to methotrexate". No particular structure is correlated with such an affinity, other than by way of example. Thus, it would be impossible for one of skill in the art to predict the subset of proteins that will bind to methotrexate.

16. Claims 91-94, 97-105, 111-122, and 125-127 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for compounds comprising structures known to recognize known receptors, does not reasonably provide enablement for compounds comprising unknown structures thought to recognize unknown receptors. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The ability to produce the full scope of receptor-ligand pairs wherein the ligands can be used as a portion of the claimed dimerizing compound would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

While the state of the art contains numerous examples of receptor-ligand pairs, many of which ligands would be easily used in the dimerizing compounds claimed, the specification provided no guidance or working examples for the production of all (or an enabling portion of the claimed genus) of new receptor-ligand pairs. The nature of the invention is such that screening procedures are available to identify such receptor-ligand pairs; however, the predictability of determining appropriate ligands and/or receptors is very low. Thus, the instant claims are not enabled to the full extent of their scope.

17. Claims 97-105 and 113-118 are rejected under 35 U.S.C. § 112, first paragraph, scope of enablement, because the specification, while being enabling for compounds or fusion proteins comprising structures known to recognize receptors or compounds with these particular affinities, does not reasonably provide enablement for compounds or fusion proteins comprising structures without such affinity for their receptors or compounds. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The ability to produce compounds and/or fusion proteins having particular affinities for their respective receptors and/or ligands would require undue experimentation.

The factors to be considered in determining whether undue experimentation is required are summarized above.

As noted in the specification by way of example, dexamethasone binds rGR with an affinity around 5 nM and methotrexate binds DHFR with an affinity in the picomolar range. There are other examples in the art where ligands bind receptors and/or proteins with affinities in the nanomolar and picomolar range. However, the instant specification has not described so as to enable the production of higher affinity ligand-receptor pairs. While it is true that mutagenesis and screening may produce a higher affinity protein-ligand interaction, this experimentation is wholly unpredictable. Thus, the instant claims are not enabled to the full extent of their scope.

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

18. Claims 91-94 and 97-100 are rejected under 35 U.S.C. § 102(b) as being anticipated by Khawli *et al.* (see IDS #4). The instant claims are drawn to compounds H1-Y-H2 where H1 is methotrexate and H2 is anything that binds a receptor or protein (based on the lack of clarity of the term dexamethasone analog as noted above in the rejection under 35 U.S.C. § 112, second paragraph) with an affinity less than 100 μM.

Khawli *et al.* teach methotrexate-conjugated antibodies (see column 16, line 5). More specifically in Example 20, methotrexate is conjugated to a monoclonal antibody that recognizes an antigen found in human pancreatic tumors. Based on the common scientific knowledge of the high affinity of monoclonal antibodies and based on the effectiveness of the protocol taught by Khawli *et al.* (see column 17, lines 52-55), an inherent affinity of the described H2 moiety is at least 100 μM.

Allowable Subject Matter

19. The instant application describes a yeast three-hybrid system with a specific example using a dexamethasone-methotrexate heterodimer. Yeast three-hybrid systems are useful in the discovery of previously unknown receptors for known ligands through efficient cDNA library screening. This system is described in USPN 5,928,868 (Liu *et al.*, IDS #4) using a dexamethasone-FK506 heterodimer, among others (see also Licitra *et al.* in IDS #4). While Licitra *et al.* teach the usefulness and broad applicability of their system, even specifically teaching the usefulness of high affinity ligand-receptor pairs (see page 12820), no indication of

the usefulness of methotrexate as a ligand is found. Methotrexate is well known to have high affinity (picomolar range) for its receptor/protein, dihydrofolate reductase (DHFR). Pollock *et al.* (see PTO-892) is a useful review of the state of the art of yeast three-hybrid systems.

Conclusion

20. Claims 91-127 are not allowed for the reasons identified in the numbered sections of this Office action. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kathleen M Kerr whose telephone number is (703) 305-1229. The examiner can normally be reached on Monday through Friday, from 8:30am to 5pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathupura Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Kathleen Kerr

KMK
December 28, 2002